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The Impact of Sex and Gender on Innovation and Health Technology

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The Impact of Sex and Gender on Innovation and Health Technology[1]

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Throughout history, there has been an unsettling partiality for men in the healthcare industry. A leading example highlighting this problem is heart disease and the long history of its treatment plans directed towards men. In 1982, a study on cholesterol and its impact on cardiovascular disease involved 12,866 men and ***no*** women.[2] In addition to clinical trials, the focus on men was also evident in the area of medical education, where a diverse group of diseases, progression, symptomatology and treatments were described with little to no comment as to whether sex differences were apparent.[3] To this day, the implications of heart disease as being a man's disease are significant, since women continue to be under recognized by health professionals when they have symptoms of heart disease. Since women are less likely to be tested for and diagnosed with heart disease due to uncommon symptoms, the available data and clinical course data continue to be two areas that are understudied. In addition to the diagnostic problem, the available treatment options continue to be tailored to men and thus are less suitable for women.

In 1993, the National Institutes of Health (NIH) passed the NIH Revitalization Act, which ensured the inclusion of women and minorities in clinical research.[4] Clinical trials must

[1] Adapted from a presentation, *The Impact of Gender and Sex on Innovation and Health Technology,* by Dima Elissa, MBA, CEO and Founder VisMed3D, AMWA Tech and Innovation Lead, DI&I Sector and Dr, Neelum Aggarwal, Co-Leader of the Rush University Medical Center Alzheimer's Disease Center Clinical Core and Associate Professor of Neurological Sciences at the 2016 Annual Jaharis Symposium, DePaul College of Law (Mar. 15, 2016).
[2] Vidhi Doshi, *Why heart disease still considered "man's disease"?*, GENETIC LITERACY PROJECT (Nov. 2, 2015), https://geneticliteracyproject.org/2015/11/02/heart-disease-still-considered-mans-disease/.
[3] *Id.*
[4] National Institutes of Health Revitalization Act of 1993, S. 1, 103rd Cong. § 492B (a) (1993).

include women and minorities unless there is a clear and compelling rationale and justification for exclusion.[5] For example, excluding women from prostate studies would be an adequate rationale, but cost is not an acceptable reason for exclusion. In addition to including women and minorities, researchers must design and carry out trials in a manner that sufficiently provides valid analysis based upon the proposed research plan. The plan and/or proposal must outline the composition of the study population and describe why that particular population was chosen.

Why is Heart Disease a "Man's Disease"?

In the 1700s, the heart was linked to emotion, particularly anger.[6] In the late nineteenth century, William Osler, a physician, challenged this idea by arguing that heart disease was caused by stress.[7] He identified a typical heart disease patient as a "keen and ambitious man, the indicator of whose engine is always 'full speed ahead."[8] By the 1950s, even though heart disease had been linked to diet, exercise, and other physical factors, it was still considered only a man's disease and lifestyle recommendations if made, were directed to at risk men.[9]

Fast forward to a 1995 study on aspirin and heart disease.[10] Even though the NIH Revitalization Act was passed in 1993, which stated that women and minorities must be

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[5] *NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research*, U.S. DEP'T OF HEALTH & HUMAN SERV. – NAT'L INST. OF HEALTH, https://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm (last visited Jan 6, 2018).
[6] Vidhi Doshi, *Why Doctors Still Misunderstand Heart Disease in Women: Reconsidering the "typical" heart-attack symptoms*, THE ATLANTIC (Oct. 26, 2015), http://www.theatlantic.com/health/archive/2015/10/heart-disease-women/412495/#article-commentsGender Differences.
[7] *Id.*
[8] *Id.*
[9] *Id.* at 3.
[10] *Id.*

represented in clinical trials,[11] this study recruited over 22,000 persons, and only involved men.

Medical illustrations, an important area in medical education and training, also had a noticeable male focus.[12] Harlan Krumholz, the editor of the *New England Journal of Medicine*, recalled the iconic drawings of Frank Netter, one of the most famous medical illustrators of the twentieth century-Netter's illustrations, and stated there were very few illustrations, that depicted a woman with heart disease."[13]

Sex Differences

A. Structural Differences of the Heart

While there are no statistically significant sex-related differences in the heart during puberty, there are differences in male and female hearts *after* puberty. Notably, heart mass is fifteen to thirty percent bigger in males than in females[14] and thought to be due to myocytes undergoing a greater degree of hypertrophy in males compared to females.[15] It is unclear whether this solely occurs due to the role of sex hormones, particularly estrogen, which provides cardio-protection[16] or whether genes located on the X chromosomes are expressed at higher levels in females than in males.[17] In addition, males express genes on the Y chromosome, which are clearly not present in females.[18] Apart from the genetic contributions, other likely proteins

[11] *NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research*, *supra* note 5.
[12] *Id.*
[13] *Id.*
[14] Leslie A. Leinwand, *Sex is a potent modifier of the cardiovascular system,* 112 THE J. OF CLINICAL INVESTIGATION 302, 302 (Aug. 2003), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC166308/pdf/JCI0319429.pdf.
[15] *Id.*
[16] *Id.* at 304.
[17] *Id.* at 305.
[18] *Id.*

that may contribute to sex differences in cardiac structure and functioning, include calmodulin-dependent protein kinase, Akt, glycogen synthase kinase 3B, and myocyte enhancer factor 2 signaling proteins.[19]

Another sex-related difference in the structure of the heart is the anatomic location of major vessels. Even though vessels are composed of the same cell types for both men and women, their functions vary. According to several studies, left ventricular systolic function influenced by the anatomic geometry of the left ventricle and left ventricle geometry differs between men and women.[20] The dual-chambered pump is smaller in women than in men, which translates into a smaller stroke volume and thus, a lower cardiac output.[21] In addition, the heart rate (also known as the rate of pumping) is greater in females than in males, except in utero.[22]

One study on atherosclerosis that evaluated age-related left ventricle (LV) remodeling found that as patients age, the LV responds differently in its mass and volume between men and women.[23] According to the results from the *The Multi-Ethnic Study of Atherosclerosis* (MESA) study, LV mass was found to be increased in men (8.0 g) and decreased in women (-1.6 g) and the LV end-diastolic volume decreased for both men (-9.8) and women (-13.3) per decade.[24]

There are also differences in the electrical activity of cardiac myocytes.[25] Typically,

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[19] *Id.*
[20] Virginia H. Huxley, *Sex and the cardiovascular system: the intriguing tale of how women and men regulate cardiovascular function differently,* 31 THE AM. PHYSIOLOGICAL SOC'Y 17, 19 (Nov. 28 2007), http://www.physiology.org/doi/pdf/10.1152/advan.00099.2006.
[21] *Id.* at 18.
[22] *Id.*
[23] John Eng et al., *Adverse Left Ventricular Remodeling and Age Assessed with Cardiac MR Imaging: The Multi-Ethnic Study of Atherosclerosis,* 278 RADIOLOGY 714, 715 (Mar. 2016), http://pubs.rsna.org/doi/10.1148/radiol.2015150982.
[24] *Id.* at 720.
[25] Huxley, *supra* note 20.

women's electrocardiography (ECG) tests show a longer QT interval after puberty compared to men.[26]

Even the composition of the blood circulating in the body vary between men and women. Females have a lower number of circulating red blood cells per unit volume of plasma, often noted as a lower hematocrit.[27] The amount of high-density lipoprotein (HDL) is higher and triglycerides are lower in females, pre-menopause, than in males and is associated with a lower incidence of cardiovascular disease.[28] However, after menopause, the lipoprotein profile of females becomes more atherogenic and is correlated with the higher incidence of heart disease in that population.[29] These physiological changes between the sexes is important for clinical screening protocols, treatment and clinical trial design and data analyses.

Sex-related differences also appear during cardiovascular stress. Generally, men respond to cardiovascular stress by increasing vascular resistance, which manifests as an increase in blood pressure.[30] On the other hand, women respond to stress by increasing their heart rate, which increases cardiac output.[31] In addition, blood pressure control through the baroflex system differs between men and women.[32] Men have higher plasma norepinephrine levels than women[33] and women have reduced sympathetic activity and parasympathetic activity relative to men.[34] Consequently, women are more vulnerable to orthostatic hypotension and fainting than

[26] *Id.*
[27] *Id.*
[28] *Id.*
[29] *Id.*
[30] *Id.* at 18.
[31] *Id.*
[32] *Id.*
[33] *Id.*
[34] *Id.*

men due to their body position and fluid shifts.[35] Even though the mechanisms underlying sex differences are not understood, estrogen and testosterone play a significant role, with testosterone in the development of and estrogen in the protection against high blood pressure.[36]

B. Sex Differences in the Regulation of Blood Pressure

According to Reckelhoff, "[m]en are at a greater risk for cardiovascular and renal disease than are age-matched, premenopausal women."[37] According to recent studies in which 24-hour ambulatory blood pressure monitoring techniques were used, men had higher blood pressure than women by about 6–10 mmHg.[38] However, after menopause, women had higher blood pressure levels than men.[39] One possible explanation for this finding is that pre-menopause, estrogen is responsible for stimulating nitric oxide production, thereby activating a vasodilator pathway, and regulating blood pressures. At or after menopause, the loss of estrogen can result in the dysregulation of this pathway, which subsequently can increase blood pressures.[40]

C. Sex Hormones

Sex hormones are also thought to cause the variation in cardiovascular effects between men and women. While premenopausal women have a low incidence of cardiovascular disease compared to men, the incidence level rises to the same or even more for women post-menopause.[41] Both androgens and estrogens influence a multitude of vascular biological

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[35] *Id.*
[36] *Id.* at 19-20.
[37] Jane F. Reckelhoff, *Gender Differences in the Regulation of Blood Pressure,* 37 HYPERTENSION 1199, 1199 (May 2001), http://hyper.ahajournals.org/content/37/5/1199.full.
[38] *Id.*
[39] *Id.*
[40] *Id.* at 1201.
[41]Gorazd Drevensek, *The Role of Sex Hormones in the Cardiovascular System*, INTECHOPEN at 31 (Feb. 8, 2012), http://cdn.intechopen.com/pdfs-wm/27778.pdf. *See also* Cristiana Vitale et al., *Gender differences in the cardiovascular effects of hormones,* 6 FUNDAMENTAL & CLINICAL

processes and their cardiovascular effects are multifaceted."[42] Consequently, high androgen levels and low estrogens plasma concentrations have been respectively related to the increased impact of CVD in men and in postmenopausal women.[43]

In addition, risk factors have varying degrees of weight between men and women, especially in the presence of an ovarian deficiency state, when the drop in sex hormones negatively affects several conditions such as hyperinsulinaemia, obesity, high cholesterol and blood pressure.[44] After menopause, women develop a pro-atherogenic lipid profile because of impaired estrogen production"[45] increased tendency for a sedentary lifestyle and both body fat distribution and glucose metabolism increase the risk of CVD.

In terms of glucose metabolism, while the risk of CVD in both men and women is significantly increased in diabetes cases and with an altered glucose metabolism, the probability of future cardiovascular events is greater in women with diabetes than in men, especially when the disease is associated with increased blood pressure.[46] Diabetic women have lower estrogen levels than non-diabetic women, and it has been shown to cause a progressive decline in glucose-stimulated insulin secretion, and to increase insulin resistance by reducing insulin sensitivity.[47]

Some earlier studies showed that hormone replacement therapy (HRT) was beneficial for primary cardiovascular prevention.[48] Conversely, a post-analysis of the results of the

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PHARMACOLOGY 532, 675 (Feb. 22, 2010), http://onlinelibrary.wiley.com/doi/10.1111/j.1472-8206.2010.00817.x/epdf.
[42] Vitale, *supra* note 41.
[43] *Id.*
[44] *Id.* at 679.
[45] *Id.*
[46] *Id.*
[47] *Id.*
[48] *Id.*

Framingham Study clearly showed that HRT is protective in younger women, but can be harmful to those starting treatment late, and especially after the age of sixty.[49]

Estrogen may be beneficial for both genders, but the effect of androgens differs between men and women.[50] For women, the effect of testosterone depends on background estrogen levels, whereas for men, the effect of testosterone depends on its aromatization into estradiol.[51] While androgen replacement in women does not increase cardiovascular risk, replacement therapy in men may be beneficial, but long-term interventional studies with physiological androgen doses are lacking and therefore warranted.[52]

NIH/FDA Guidelines & Funding Changes

The NIH Revitalization Act of 1993 ensured the inclusion of women and minorities in clinical research, which also includes clinical trials.[53] In addition, the statute provides that when women and minorities are included as subjects, the trial must be designed and carried out in a manner sufficient to provide for valid data analysis.[54] An issue arises with this provision because clinical researchers do not conduct internal analyses stratifying their results between men/women, female/male, race routinely or *report these data results* in the final publication.

In May 2014, the NIH took a more focused approach to identify steps to address sex differences in preclinical research.[55] As part of new policies, the NIH "require[d] applicants to

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[49] *Id.*
[50] *Id.* at 681-82.
[51] *Id.* at 682.
[52] *Id.*
[53] National Institutes of Health Revitalization Act of 1993, S. 1, 103rd Cong. § 492B (1993).
[54] *Id.*
[55] *Filling the Gaps: NIH to Enact New Policies to Address Sex Differences*, U.S. DEP'T OF HEALTH & HUMAN SERV. – NAT'L INST. OF HEALTH OFFICE OF RESEARCH ON WOMEN'S HEALTH, (May 14, 2014), https://orwh.od.nih.gov/about/director/messages/nih-policies-sex-differences/.

report their cell and animal inclusion plans as part of preclinical experimental design"[56] and note this in their grant applications. In theory this policy would promote "a balanced approach to addressing male and female differences in cells and animals."[57]

In June 2015, the NIH took the initiative to include sex as a variable in research by announcing some changes to the "instructions for scientists applying for NIH funding" and by "revising criteria for the reviewers who judge the funding applications."[58] The NIH highlighted "that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies."[59] Thus, the NIH made sex a fundamental biological variable that must be considered in research to ensure both men and women receive full benefits from medical research and also guide further research. Further, "[s]cientists proposing to study only one sex will be required to provide strong justification from the scientific literature, preliminary data, or other relevant considerations."[60]

In 2016, a new law mandated that every funding application submitted to the NIH after January 1, 2016, would need to describe the research or study proposed in the context of sex and gender.[61] The reasoning behind this new law was to ensure that research not only gave thought about this criteria, but that preclinical research studies include women. It is problematic to only have preclinical studies on one sex or gender, especially with studies that are intended to inform understanding of diseases and conditions affecting both sexes. Failure to account for sex as a

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[56] *Id.*
[57] *Id.*
[58] *Studying Sex to Strengthen Science*, NAT'L INST. OF HEALTH OFFICE OF RESEARCH ON WOMEN'S HEALTH, https://orwh.od.nih.gov/resources/pdf/orwh-igiant-factsheet-studying-sex.pdf.
[59] *Id.*
[60] *Id.*
[61] *Id.*

biological variable may undermine the rigor, transparency, and generalizability of research findings to the general population."[62]

The Food and Drug Administration (FDA) Office of Women's Health (OWH) also has its mission aligned to "[a]dvocate for the inclusion of women in clinical trials"[63] and therefore, all clinical trials must consider sex and gender in order to obtain FDA approval. As such, the FDA outlined an action plan in Section 907 of the FDA Safety and Innovation Act (FDASIA), which had the following three overarching priorities to help direct their activities:

1. Quality: to improve the completeness and quality of demographic subgroup data;

2. Participation: to identify barriers to subgroup enrollment in clinical trials and employ strategies to encounter greater participation;

3. Transparency: to improve the public availability of demographic subgroup data."[64]

In addition to the above priorities, enhancing innovation in the areas of drug and medical devices have also been part of the mission of the FDA.[65]

A. Impact & Implications

Even with new innovations such as drugs and devices, there still exists an unsettling partiality for men in healthcare.

a. <u>New Innovations</u>

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[62] *Including Women and Minorities in Clinical Research,* U.S. DEP'T OF HEALTH & HUMAN SERV. – NAT'L INST. OF HEALTH OFFICE OF RESEARCH ON WOMEN'S HEALTH, https://orwh.od.nih.gov/clinical/women-and-minorities/.

[63] *Protecting and Advancing Women's Health,* FDA OFFICE OF WOMEN'S HEALTH at i, https://www.fda.gov/downloads/scienceresearch/specialtopics/womenshealthresearch/ucm135376.pdf.

[64] *FDASIA Section 907: Inclusion of Demographic Subgroups in Clinical Trials,* FDA, https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/ucm389100.htm.

[65] *Protecting and Advancing Women's Health, supra* note 63.

i. Drugs

While the FDA is engaged in both data collection and policy development, it is still important to include women in all stages of NIH-sponsored trials.[66] These trials can help clarify the understanding of diseases, treatment regimens, and care delivery.[67] Women make up one of the most frequent subgroups of patients for a variety of medical conditions.[68] A primary reason for the past exclusion of women in clinical trials was the concern of exposing a future fetus to experimental drugs.[69] While still subject to concern today, this conception was challenged in the 1990s, when HIV-infected women found themselves ineligible to participate in trials of new antiviral therapies.[70] This issue was exacerbated by the fact that there were very few alternative treatments available.[71] The FDA has addressed this issue by formulating steps to facilitate the inclusion of premenopausal women into clinical trials.[72] To ensure safety, these steps are subject to certain exceptions. In addition to the challenge of treating women before they have reached menopause, there lies the even more daunting challenge of treating women who are already pregnant. There remains widespread caution in treating pregnant women with investigational

[66] U.S. Senate Comm. – Health, Educ., Labor & Pensions, *Democratic Senate and House Leaders Request GAO Study on Inclusion of Women in NIH-Supported Clinical Trials* (Apr. 30, 2014), https://www.help.senate.gov/ranking/newsroom/press/democratic-senate-and-house-leaders-request-gao-study-on-inclusion-of-women-in-nih-supported-clinical-trials.
[67] *Id.*
[68] Jesse A. Berlin & Susan S. Ellenberg, *Inclusion of women in clinical trials*, 7 BMC MED. 1, 1 (Oct. 9, 2009).
[69] *Id.* at 2.
[70] *Id.*
[71] *Id. See also* Haley Gorenberg & Amanda White, *Off the Pedestal and into the Arena: Toward Including Women in Experimental* Protocols, 19(1) REV. LAW SOC. CHANGE 205-46 (1991-92).
[72] Berlin, *supra* note 68. *See also* R.B. Merkatz & S.W. Junod, *Historical background of changes in FDA policy on the study and evaluation of drugs in women*, 69 ACAD. MED. J. ASS'N AM. MED. COL. 703, 703-07 (Sept. 1994).

drugs to protect the developing fetus.[73] This leaves pregnant women with very little information when making a decision on treatment because there is no past data of the potential effects of specific experimental treatments on pregnant women.

One exception to this are the experimental trials with the H1N1 flu vaccine.[74] These followed the recommendation of the Center for Disease Control and Prevention and the American College of Obstetricians and Gynecologists based on a 2009 study in the Lancet Medical Journal, which found that pregnant women were four times more likely to be hospitalized from H1N1 than the general population.[75] Because pregnant women are considered to be in the high-risk group for this infection, the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) conducted a national survey of 1,032 pregnant women who either were or were not vaccinated between 2009 and 2012.[76] The study concluded that "pregnant women who were vaccinated were no more likely to have a miscarriage, a baby born with a birth defect or a baby born smaller than normal, compared with a women who did not get a vaccination."[77]

The issue of the under inclusion of women in clinical studies of experimental drugs was addressed in 2001 by the Government Accountability Office (GAO). The GAO reported that although women made up over fifty percent of the study participants for new drug applications,

[73] Berlin, *supra* note 68, at 3.
[74] *Id.*
[75] *Id. See also* Annie Gowen, *Pregnant Women in D.C. Area Cautious About Swine Flu Vaccinations*, WASHINGTON POST (Aug. 20, 2009), http://www.washingtonpost.com/wp-dyn/content/article/2009/08/19/AR2009081903728.html.
[76] Marie Ellis, *H1N1 flu: pregnant women can safely take vaccine*, MEDICAL NEWS TODAY (Sept. 24, 2013), https://www.medicalnewstoday.com/articles/266513.php.
[77] *Id.*

only twenty-two percent of early stage clinical trials were made up of women.[78] This is cause for concern, as phase 1 trials are structured around the assessment of safety and help set initial dosing levels.[79] This same problem resurfaced in the 2006 and 2007 reviews of clinical trials that were done to support the approval of new drugs.[80] The review revealed that women were still underrepresented in phase 1 trials, compromising approximately only one-third of participants.[81]

ii. Devices

It has been over twenty years since the enactment of the NIH Revitalization Act, and there still remains a reluctance to conduct sex-specific analyses and report sex-based differences in medical device clinical trials.[82] As a result, there remains a dearth of information in regards to potential sex differences in dosing, safety, and effectiveness, some of which could have been detected in earlier stages of research had females been included.[83] In December 2011, the FDA issued a draft guidance entitled *Evaluation of Sex of Differences in Medical Device Clinical Studies,* which advocated for an adequate inclusion of women in trials and the reporting of the analysis of sex-based differences.[84] In its guidance, the FDA stressed the importance of such

[78] U.S. Senate Comm. – Health, Educ., Labor & Pensions, *supra* note 66; *see also* General Accounting Office, *Women's Health: Women Sufficiently Represented in New Drug Testing, but FDA Oversight Needs Improvement* (July 6, 2001) (GAO-01-754).
[79] *Id.*
[80] U.S. Senate Comm. – Health, Educ., Labor & Pensions, *supra* note 66.
[81] *Id.*
[82] Martha R. Nolan & Thuy-Linh Nguyen, *Analysis and Reporting of Sex Differences in Phase III Medical Device Clinical Trials – How Are We Doing?*, 22 J. WOMEN'S HEALTH 399, 399 (May 2013).
[83] *Id.* at 400.
[84] *Id. See also* Guidance for Industry and FDA Staff, *Evaluation of Sex-Specific Data in Medical Device Clinical Studies*, FDA (Aug. 22, 2014), https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM283707.pdf.

representation in medical device clinical trials.[85] A study of the progression in sex-specific analysis and reporting over time was conducted by utilizing the website ClinicalTrials.gov.[86] The website was chosen because it is one of the fundamental resource for seeking information about clinical trials and their study results.[87] The results of the search yielded eighty-seven studies with a majority (ninety-seven percent) reporting the sex of their participants.[88] While the average representation of women in device clinical trials was fifty percent, the average rate of female participation was categorized by target disease category and was thirty-four percent lower in studies on cardiovascular disease than in all other categories.[89] A similar study involving cardiovascular devices that obtained premarket approval by the FDA was conducted from 2000 to 2007. The results concluded that women made up less than one-third of the subject population.[90] It is important to note that although the aforementioned studies demonstrate that women are underrepresented as participants in clinical device studies, many of these reviews are not required to report sex-specific analysis.[91] This reveals not only a persistent pattern of women being underrepresented in cardiovascular device trials but also shows a lack of enforcement by the FDA in regulating its own reporting directives.[92]

A similar study was conducted on the difference between sexes in randomized trials of

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[85] Nolan, *supra* note 82.
[86] *Id.* at 400.
[87] *Id.*
[88] *Id.*
[89] *Id.*
[90] *Id. See also* S. Sanket Dhruva et al., *Gender bias in studies for Food and Drug Administration premarket approval of cardiovascular devices*, 4 CIRC CARDIOVASC QUAL OUTCOMES 165-71 (Mar. 2011).
[91] Nolan, *supra* note 82.
[92] *Id.*

implantable cardioverter-defibrillator (ICD) therapy in high-risk patients.[93] The AVID trial was a large U.S. study that enrolled patients who had survived cardiac arrest due to ventricular fibrillation, syncopal VT, or symptomatic VT[94] and yet, in this important study, only twenty-one percent of the recruited patients were women.[95]

B. NIH Funding Rules/Considerations

The NIH Revitalization Act also has implications on the potential for investments needed to conduct certain clinical studies. In 2014, the NIH invested $10.1 million to assist eighty-two grantees in conducting research exploring the effects of sex in preclinical and clinical studies.[96] This program was launched in the fiscal year of 2013 under leadership from the Office of Research on Women's Health.[97] The grantees' projects spanned a wide range of scientific topics including, but not limited to (1) basic immunization, (2) cardiovascular physiology, (3) neural circuitry, and (4) behavioral health.[98] The investment was meant to encourage researchers to study both sexes as a fundamental variable in research.[99] Including both sexes in clinical studies is important as an overreliance on male subjects in preclinical research can obscure key findings related to sex that could help guide later studies.[100] Discussing the importance of the program, Janine Austin Clayton, the NIH Associate Director for Women's Health Research, remarked: "[t]his funding

[93] Yong-Mei Cha et al., *Arrhythmias in Women Diagnosis and Management*, MAYO CLINIC SCIENTIFIC PRESS at 29 (2014).
[94] *Id.*
[95] *Id.*
[96] Nat'l Inst. of Health, N*ew supplemental awards apply sex and gender lens to NIH-funded research*, U.S. DEP'T OF HEALTH & HUMAN SERV. (Sept. 23, 2014), https://www.nih.gov/news-events/news-releases/new-supplemental-awards-apply-sex-gender-lens-nih-funded-research.
[97] *Id.*
[98] *Id.*
[99] *Id.*
[100] *Id.*

strategy demonstrates our commitment to moving the needle toward better health for all Americans, while helping grow our knowledge base for both sexes and building research infrastructure to aid future studies."[101] She further stated, "scientists receiving these awards have approached their research questions with fresh thinking, and are looking for innovation and discovery through a new lens."[102]

C. Evidence-Based Examples of Gender and Sex in Healthcare Treatments

a. Cardiology

There are many known differences between men and women in heart disease, but the reason is still unknown, which is a problem. The 1980s illustrated the complete lack of inclusion of women in mainstream medical studies.[103] Two of the major cardiovascular studies include (1) the Physicians' Health Study on the effects of aspirin on cardiovascular disease, in which 22,071 men and zero women physicians were enrolled,[104] and (2) the Multiple Risk Factor Intervention Trial (MRFIT)—a randomized trial evaluating correlations among blood pressure, smoking, cholesterol, and coronary heart disease—in which 12,866 men and zero women were participants.[105]

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[101] *Id.*

[102] Nat'l Institutes of Health, N*ew supplemental awards apply sex and gender lens to NIH-funded research*, U.S. DEP'T OF HEALTH & HUMAN SERV. (Sept. 23, 2014), https://www.nih.gov/news-events/news-releases/new-supplemental-awards-apply-sex-gender-lens-nih-funded-research.

[103] Londa Schiebinger, *Women's health and clinical trials*, 112 J. CLINICAL INVESTIGATIONS 973, 973 (Oct. 1, 2003).

[104] Steering Comm. of the Physicians' Health Study Research Group, *Final report on the aspirin component of the ongoing Physicians' Health Study*, *Steering Committee of the Physicians' Health Study Research Group*, 321 NEW ENG. J. MED. 129 (July 20, 1989).

[105] Multiple Risk Factor Intervention Trial Research Group, *Multiple risk factor intervention trial: Risk factor changes and mortality results*, 248 JAMA 1465 (1982). *See also* Schiebinger, *supra* note 103.

A more recent study involved a federally funded analysis of MRI scans of the hearts of approximately 3,000 male and female adults.[106] The MRIs showed a significant difference in the way male and female hearts age over time.[107] Specifically, as men age, the heart muscle that surrounds the main heart chamber grows bigger and thicker.[108] In contrast, as women age, the same chamber either retains its size or gets smaller.[109] Although these results fail to explain the cause of the difference between the sexes, they may still illustrate the varying forms of heart failure in men and women, which would require sex-specific treatments.[110] Doctor John Eng, a lead investigator of the study, concluded that a "[t]hicker heart muscle and smaller heart chamber volume both portend heightened risk of age-related heart failure, but the gender variations we observed mean men and women may develop the disease for different reasons."[111] Because heart failure is currently treated by the prescription of medication designed to reduce the thickness of the heart muscle over time and because women's hearts may shrink with age, this treatment method is less beneficial to women patients.[112]

b. Neuro (degenerative)

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that disproportionately affects women in both prevalence and severity.[113] Symptoms include memory

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[106] *Male and Female Hearts Don't Grow Old the Same Way*, JOHNS HOPKINS MED. (Oct. 20, 2015), https://www.hopkinsmedicine.org/news/media/releases/male_and_female_hearts_dont_grow_old_the_same_way.
[107] *Id.*
[108] *Id.*
[109] *Id.*
[110] *Id.*
[111] *Id.*
[112] *Id.*
[113] Christine L. Carter et al., *Sex and Gender Differences in Alzheimer's Disease: Recommendations for Future Research*, 21 J. WOMEN'S HEALTH 1018, 1018 (2012).

loss, cognitive deficits, and behavioral changes.[114] Although AD was identified over one-hundred years ago, there is still little known about what triggers it.[115] Because of this, the current available treatments are unable to slow or reverse the damage it causes.[116] The chemical nature of AD is characterized by the accumulation of two proteins in the brain: amyloid and tau.[117] Amyloid precursor proteins are divided into smaller amyloid fragments through an unknown process.[118] These fragments accumulate and cause plaque deposits to collect in the extracellular spaces, thus disrupting nerve-to-nerve communications and causing fibers to swell as well as other morphologic changes.[119] Tau is a protein that typically binds and stabilizes components of the neurons of the brain.[120] In AD, tau accumulation forms neurofibrillary tangles that can disrupt important signaling.[121] These two processes cause selective neuronal cell death, contributing to the disease's progression.[122]

AD's disproportionate effect on women can stem from the difference in biological mechanisms between sexes, including brain anatomy, age-related declines in brain volume, or brain glucose metabolism.[123] In the United States, approximately 3.4 million women over the age of sixty-five are affected by AD compared to 1.8 million men.[124] It is speculated that in addition to the above-mentioned biological difference, the longevity of women's lives may play a role.[125]

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[114] *Id.*
[115] *Id.*
[116] *Id.*
[117] *Id.*
[118] *Id.*
[119] *Id.*
[120] *Id.*
[121] *Id.*
[122] *Id.*
[123] *Id.*
[124] *Id.*
[125] *Id.* at 1019.

One study compared global cognitive function to measures of plaque and tangle pathology derived from brain autopsies.[126] AD pathology was much more likely to be associated with dementia in women than men. Additionally, it was found that women had nearly three times the odds of being diagnosed with AD.[127] AD pathogeneses may also be affected by a change in metabolisms caused by sex hormones.[128] Estrogen is known to serve as a brain protectant, and its loss of production during menopause may be responsible for deficits in brain metabolism, leading to a higher risk of AD.[129] With the relationship between gender differences and the onset of AD still ill-defined, it is important to gain more knowledge on the interplay between genetic, hormonal, and environmental factors.[130]

c. Ortho

Women have a higher rate of osteoporosis-related hip fractures than men.[131] There are many quantitative differences between how men and women develop common musculoskeletal disorders. Anterior cruciate ligament injuries occur two to eight times more frequently in women than men.[132] Women are five to eight times more likely to suffer an ACL injury than men in high-intensity sports that require sudden changes in motion.[133] Women are twice as likely to sprain their ankles than men and are generally more susceptible than men to develop osteoarthritis of the

[126] *Id.*
[127] *Id.*
[128] *Id.*
[129] *Id.*
[130] *Id.*
[131] *Sex and musculoskeletal health: differences between males and females extend to their bone and joint conditions*, AM. ACAD. OF ORTHOPAEDIC SURGEONS (June 1, 2015), http://newsroom.aaos.org/media-resources/Press-releases/sex-and-musculoskeletal-health-differences-between-males-and-females-extend-to-their-bone-and-joint-conditions.htm.
[132] *Id.*
[133] *Id.*

knee.[134] Women may be more vulnerable to ligament tears because of the reproductive hormones that affect joint laxity.[135] When looking at orthopedic ailments in relation to an increase in age, women are more likely to develop osteoporosis than men.[136] This leads to a higher risk of hip, wrist, and vertebral spine fractures.[137]

d. Autoimmune

An autoimmune disease is one in which the body produces autoantibodies that attack normal healthy cells by mistake.[138] While autoimmune diseases affect both men and women, the majority (approximately seventy-five percent) are women.[139] Specifically, autoimmune diseases are one of the leading causes of death and disability in women sixty-five and younger.[140] While there is not yet an exact reason why women are more susceptible to autoimmune diseases than men, there are a few probable theories.[141] First, women may be at a higher risk of autoimmune diseases because of their more sophisticated immune systems.[142] As there is a correlation between inflammation and autoimmune disease, the fact that women's inflammatory responses are stronger than men's leads to a potential for more frequent disease. Second, women's hormones may play a role in the potential for disease and autoimmune flare ups often associated with hormonal

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[134] *Id.*
[135] Lisa Esposito, *No Bones About it: Men and Women Aren't Equals in Orthopedics*, U.S. NEWS & WORLD REPORT (July 22, 2015, 9:47 AM), https://health.usnews.com/health-news/patient-advice/articles/2015/07/22/no-bones-about-it-men-and-women-arent-equals-in-orthopedics
[136] *Id.*
[137] *Id.*
[138] U.S. Dep't of Health & Human Serv., *Autoimmune diseases*, WOMEN'S HEALTH.GOV, https://www.womenshealth.gov/a-z-topics/autoimmune-diseases.
[139] Krisha McCoy, *Women and Autoimmune Disorders*, EVERYDAY HEALTH (Dec. 20, 2012), https://www.everydayhealth.com/autoimmune-disorders/understanding/women-and-autoimmune-diseases.aspx
[140] *Id.*
[141] *Id.*
[142] *Id.*

fluctuations.[143] Hormonal fluctuations can occur during pregnancy, the menstrual cycle, or when using certain contraceptives.[144] In addition to these theories, there are a multitude of autoimmune diseases that significantly affect women over men. These include Hashimoto's thyroiditis, Graves' disease, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus (lupus), and rheumatoid arthritis.[145]

e. Renal

In the field of nephrology, women seem to be better protected from developing end-stage renal disease (ESRD) than men.[146] In a community-based screening, it was found that ESRD remained low during the reproductive years and began to rise ten years later in women than in men.[147] Further, the average age when dialysis treatment is started was found to be higher in women than in men.[148] As kidney function deteriorates with age, the extent of age-related glomerular filtration rate (GFR) varies between the sexes.[149] Additionally, a recent study with more than 200,000 patients receiving dialysis showed that men were more likely than women to be on dialysis if they had advanced kidney disease (fifty-nine percent men and forty-one percent women).[150] This observation does not shed light on underlying reasons or motivation for continuing or stopping treatment; however, it illustrates disparities in treatment. Many of the

[143] *Id.*
[144] *Id.*
[145] *Id.*
[146] Kunitoshi Iseki, *Gender differences in chronic kidney disease*, 74 KIDNEY INT'L 415, 416 (Aug. 2008), http://www.sciencedirect.com/science/article/pii/S0085253815533516.
[147] *Id.*
[148] *Id.*
[149] *Id.*
[150] Joseph Brownstein, W*omen More Likely to Get Kidney Disease, Less Likely to Get Dialysis*, EVERYDAY HEALTH (Nov. 3, 2014), https://www.everydayhealth.com/news/women-getting-kidney-disease-but-not-dialysis/.

questions about the sexes and their proportion of ESRD diagnoses remain unanswered; therefore, it is imperative to conduct further research on this topic.

f. Hepatic

Women are more susceptible than men to developing acute liver failure, benign liver lesions, primary biliary cirrhosis, and toxin-mediated hepatotoxicity.[151] Potential reasons for this increased susceptibility may include the effect of sex hormones on oxidative and metabolic pathways, differential gene transcriptions in response to injury in women compared with men, and sex-based differences in immune regulation.[152] Women are more vulnerable than men to the negative effects of alcohol and drug use on the liver. This fact is bolstered by a Denmark study of 13,000 participants that showed the risk of development of alcohol-related liver disease increased in women who consumed between seven to thirteen beverages per week compared to men who consumed fourteen to twenty-seven beverages per week.[153] Even following the abstinence of alcohol, women with alcoholic liver disease have a more rapid progression to fibrosis.[154] Several factors may contribute to the severity of alcoholic liver disease in women, which include: (1) a higher endotoxin level; (2) increased gut permeability to endotoxins; (3) estrogen receptor concentrations within the liver; and (4) the potential activation of liver Kupffer cells by estrogen, leading to increased inflammation and necrosis.[155]

D. Sexual Orientation Reasoning Examples

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[151] Jennifer Guy & Marion G. Peters, *Liver Disease in Women: The Influence of Gender on Epidemiology, Natural History, and Patient Outcomes*, 9 GASTROENTEROLOGY & HEPATOLOGY 633, 633-35 (Oct. 2013), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3992057/pdf/GH-09-633.pdf.
[152] *Id.* at 633.
[153] *Id.* at 634.
[154] *Id.*
[155] *Id.*

It has been well established by various research projects that health disparities exist among the LGBTQIA+ community as a growing minority group. These biases are primarily rooted in bias, stigma, discrimination and other social determinants of health, rather than biological genetics or gender identity. The issues for this population group exist not only within underrepresentation in clinical trials, but also in day-to-day healthcare. These issues can be solved through expansive healthcare system changes and education changes, beginning with simple data collection and reaching as far as research project formation. The examples of issues for healthcare correlating to the sexual-orientation of patients are plentiful within these areas.

On a more general scale, the lack of data collection regarding gender identity begins with the daily practitioner. Few clinical practitioners ask about sexual orientation or gender identity during general check-ups. In locations where they do ask, practitioners have noted patient reluctance to reveal personal information regarding their sexual orientation. Conversely, the issue of physician discomfort and ignorance on the importance of the information still pervades the medical field.[156] As an example, discomfort with sharing their sexual identity can keep members of the LGBTQIA+ community from seeking preventative healthcare for HIV/AIDS, resulting in higher incidence rates in these populations.[157] This, of course, only supports negative stereotypes, which furthers problems for the community. Until and unless action is taken to educate physicians and patients on the importance of disclosing sexual identity information, this discomfort will continue to create problems for healthcare development and patient treatment.

Aside from long-term social problems, failing to collect information on a patient's sexual

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[156] Jon Q. Sanders et al., *Collecting sexual orientation and gender identity data in electronic health records: Workshop summary,* NAT'L ACAD. PRESS (2013).
[157] Dean L. Meyer, *Lesbian, gay, bisexual, and transgender health: Findings and Concerns,* 4 J. OF THE GAY AND LESBIAN MED. ASS'N 102, 111 (2002).

orientation can lead to immediate issues for them, such as prolonged delay of treatment or even incorrect diagnosis. One case study shows a fifty-year-old woman who was hospitalized for a high fever and severe chills.[158] Doctors spent hours trying to determine the source of the issue, and eventually discovered that it was an infection in the prostate gland. If the practitioners had been in the practice of collecting information on patients' sexual orientation, the woman could have received a speedier diagnosis and easier treatment. Similar examples to this exist for transgender men as well.

Many are already working to solve these problems, which (as seen in the examples) stem from social stigmas and other social issues, rather than biological problems themselves. One such proposed solution is the invention of Patient Portals, an electronic way for patients to discreetly and confidentially enter their personal information from home rather than using verbal answers to awkward or embarrassing questions. The information becomes part of the patient's medical record.[159] While solutions like this may aid the problem, the solution lies within education. Educating receptionists and physicians at medical centers and throughout clinical trials about the importance of such questions can help to provide more effective care for all people, regardless of their specified sexual-orientation.[160]

E. The Cost of Exclusion

As the reasoning for collecting data on sexual orientation grows, funding agencies have become more restrictive of their donations towards clinical trials. For example, as mentioned in previous sections, the NIH has made the inclusion of a diverse group of sex and gender a

[158] Sanders, *supra* note 156, at 8.
[159] *Id.* at 9.
[160] *Id.*

requirement for funding in many cases, and other federal health research funding organizations provide extra subsidies for demonstrated effort to include a wide range of sexual orientations and genders in research.[161] While such organizations explain that the exclusion of minority groups due to excessive cost is not acceptable, concerns about finances for projects are still an issue. Recruiting sufficient numbers of participants is difficult enough without considering a balanced sex or gender ratio, and oftentimes the inclusion of minorities results in additional costs.[162] For example, the Society for Women's Health Research guidelines have advised that research for sex differences should use women in different hormonal states,[163] which was shown to quadruple the medical research grant costs. While these higher costs upfront can discourage researchers from including a more diverse grouping of gender and sexual orientations (as well as other minorities), excluding subpopulations can lead to the misapplication of new treatment plans.[164] In the long run, this will cost even more. However, it should be noted that there is little data on this subject, since the mandated inclusion of a diverse range of sexes and genders is a relatively new concept.

E. Moving Forward

Although heart disease is sometimes thought of as a "man's disease," about the same number of women and men die each year of heart disease in the United States. Despite increases in awareness over the past decade, only fifty-four percent of women recognize that heart disease

[161] Suzanne Day et al., *Essential metrics for assessing sex & gender integration in health research proposals involving human participants*, 12 PloS One 1, 1 (2017).
[162] Beth A. Brown et al., *Challenges of recruitment: focus groups with research study recruiters*, 31 WOMEN & HEALTH 153, 159 (2001).
[163] Marietta Anthony & Mary J. Berg, *Biologic and molecular mechanisms for sex differences in pharmacokinetics, pharmacodynamics, and pharmacogenetics: Part II*, 11 JOURNAL OF WOMEN'S HEALTH & GENDER-BASED MED. 617, 619 (2002).
[164] Joy Johnson, *Sex, gender and clinical research: have you considered the possibilities?*, 5 Clinical Investigations 1 (2015).

is also a woman's number one killer.[165] While chest pain is the most common symptom of a heart attack, women can have symptoms that are not related to chest pain. Some of these subtle symptoms include unusual fatigue: sweating; shortness of breath; and neck, jaw, or back pain.[166] These subtle symptoms often make it more difficult for women to recognize that they are experiencing a heart attack, and therefore, women are less likely than men to go to the emergency room after a heart attack. There needs to be more awareness of the differences between women and men relating to the presentation of angina pectoris and ACS. Studies and guidelines should also consider sex-related differences when studying heart disease symptoms. Healthcare professionals and researchers must include women in studies so that they can better understand the biological differences between men and women that affect how they should be treated.

Research on sex and gender differences in clinical and basic science research must increase in the United States. Despite progress, many science researchers do not explore the impact of sex on disease. Many studies simply do not include women or enough women to analyze sex-based differences.[167] The lack of inclusion of both sexes and analyses of the data based on potential sex differences in all clinical and basic science research has far reaching implications. The economic costs of not diagnosing, treating or administering the appropriate

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[165] Lori Mosca et al., *Twelve-year Follow-up of American Women's Awareness of Cardiovascular Disease Risk and Barriers to Heart Health*. CIRCULATION: CARDIOVASCULAR QUALITY OUTCOMES (2010)

[166] U.S. Dep't of Health & Human Serv., *Subtle and Dangerous: Symptoms of Heart Disease in Women*, NAT'L INST. OF HEALTH, https://www.ninr.nih.gov/sites/default/files/subtle-and-dangerous-symptoms-heart-disease-in-women-booklet.pdf.

[167] Paula A. Johnson et al., *Precision Medicine: How sex and Gender Drive Innovation*, BRIGHAM & WOMEN'S HOSP. (2016), https://www.brighamandwomens.org/assets/BWH/womens-health/pdfs/precision-medicine-how-gender-drives-innovation-2016.pdf.

drugs and treatment, will continue to negatively impact utilization costs, development of effective and appropriate treatment plans and limit specific and targeted drug discovery and research initiatives.

G. AMWA Chicago Accelerator

As established by the previous sections, serious changes must be made to the systems of healthcare innovation in order to support a broader spectrum of individuals. While these changes must ultimately be made on a larger scale, independent accelerators have the potential to change the way minorities are included in clinical trials. More importantly, they have the potential to begin a revolution that will ultimately result in safer, better, and pioneering solutions in healthcare for all people.

In general, an accelerator is meant to supply new innovation and grow companies with support. In the healthcare industry, this means providing the resources necessary to succeed and eventually spur innovation. These accelerators exist around the country and focus on various sectors of healthcare.[168] For example, Dreamit Health based in New York and Philadelphia aims to help founders of companies find customers, perfect their marketing strategies, and raise funding. They offer programs to initiate new companies, and ultimately help them with the technology and development side of their ideas.[169] Another example is MATTER based in Chicago, which serves as an incubator for healthcare innovators. They help healthcare start-ups by providing a healthcare and technology experts, access to important connections, and as a whole, to accelerate the development of revolutionary healthcare technologies.[170] Some

[168] Conor Cawley, *20 Startup Accelerators Impacting the Healthcare Industry*, TECHCO (Sept. 21, 2017), https://tech.co/20-accelerators-incubators-healthcare-2017-09.
[169] DREAMIT, http://www.dreamit.com/#dreamit-programs (last visited May 11, 2018).
[170] MATTER, https://matter.health/about/ (last visited May 11, 2018).

accelerators work to specifically support minority groupings, such as women. Accelerators like Avindé in Austin[171] or The Brandery in Cincinnati support female founders for companies through connection-based or financial methods.[172]

Few accelerators, however, focus on helping companies that seek to solve the sex and gender bias in healthcare development. As this article has discussed, the inclusion of sex and gender into clinical trial is incredibly important for developing beneficial healthcare for all people. This is the goal of AMWAxcel, (AMWAxcel.com), an accelerator spearheaded by Dima Elissa, MBA and Dr. Neelum Aggarwal under the American Medical Women's Association Diversity, Inclusion and Innovation Sector focusing on creating an environment for diversity and inclusion in the spectrum of innovation.[173] Groups like this are essential to overcome both historical and existing biases in medical development. Through teamwork and collaboration of Women-in-STEM accelerators across the globe, these biases can be replaced with a new era of inclusive healthcare.

[171] Roshawnna Novellus, *31 Top Accelerators and Incubators for Women*, STARTUP FUNDING (Feb. 8, 2017), https://www.startupfunding.co/blog/31-top-accelerators-and-incubators-for-women.
[172] *13 Top Accelerators for Female Entrepreneurs*, FEMALE ENTREPRENEURS (July 1, 2015), https://femaleentrepreneurs.institute/12-top-accelerators-female-entrepreneurs/.
[173] TECHWEEK CHICAGO/2017, https://techweekchicago2017.sched.com/dima_elissa.1ucpu9ti (last visited May 11, 2018).